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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,884	04/07/1999	HAROLD J. WANEBO	58463/JPW/EM	6824

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

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02/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/287,884	WANEBO ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 20-33 are presented for examination

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/5/2007 has been entered.

Status of the Claims

Applicants' amendment filed 11/5/2007 has been received and entered into the application. Accordingly, claims 20-22, 25, and 30-31 have been amended and claims 32-41 have been cancelled.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 11/5/2007 have been fully considered but they are not persuasive. Applicants present the following arguments with respect to the 35 U.S.C. 103 rejections of the pending claims.

Firstly, with respect to the 35 U.S.C. 103 rejection of claims 20, 25, 30-31, and 34-41 as being unpatentable over Jayadev *et al.* in view of Mycek *et al.*, Applicants argue that the specification at page 52, Table 2 demonstrates that paclitaxel and C6-ceramide in combination produced unexpected, synergistic results. As such, citing MPEP 716.02(a)(I) and Merck & Co. v. Biocraft Laboratories Inc., Applicants assert that the greater that expected results demonstrated in the specification are probative that the instant claims are patentable over the cited references. However, it is the Examiner's position that the unexpected results are not commensurate in scope with the patent protection sought by Applicants. For example, the results are the result of *in vitro* cell proliferation assays whereas the claims are drawn to *in vivo* methods (*e.g.*, "...inhibiting the growth of a tumor..." [claim 20]; "...decreasing the size of a tumor..." [claim 25]; "...treating a subject afflicted with prostate cancer, pancreatic cancer, or head and neck squamous cell cancer..." [claim 31]). Further, the results in Table 2 are the result of specific doses of paclitaxel (600 ng/mL) and ceramide (25 μg/nL) administered in combination, whereas the claims are drawn to any amount of paclitaxel and C_6-ceramide administered sequentially or concomitantly that elicit a specific responses (*e.g.*, "...effective to induce at least 50% growth inhibition..." [claim 20]; "...effective to induce apoptosis..." [claim 25]; and "...effective to induce at least a 50% growth inhibition..." [claim 31]). While these *in vitro* cell proliferation results are no doubt unexpected, they are not commensurate in scope with the

claims. With respect to the apoptosis referred to in Figures 5A-5H, while claim 25 does recite induction of apoptosis as a result of administration of paclitaxel and C_6-ceramide, the claimed method is drawn to decreasing the size of a tumor by contacting the tumor with paclitaxel and C_6-ceramide, not inducing apoptosis. The only *in vivo* (as instantly claimed) result is drawn to a single tumor cell line, TU-138 (head and neck squamous cell carcinoma). See Figures 11 and 12 and discussion at pages 61-62 of the specification. However, because C_6-ceramide appears to exhibit significant tumor growth inhibitory activity, the results of combination paclitaxel and C_6-ceramide do not appear to demonstrate statistically significant superior growth inhibition versus C_6-ceramide alone.

In addition, as discussed in Spencer *et al.* (prior art of record), paclitaxel has been evaluated in combination with other antineoplastic agents (pages 805-807). Pertinent to Applicants' arguments of unexpected results, Spencer *et al.* teach that the order of administration of paclitaxel and other antineoplastic agents and incubation time before addition of a second active agent are important factors in whether or not synergism is observed. For example, when paclitaxel was administered before cisplatin, a synergistic effect was observed. However, when cisplatin was administered before paclitaxel, antagonistic interactions occurred (page 806, left column, first full paragraph). Similarly, when human cancer cell lines were exposed to paclitaxel before doxorubicin, a sub-additive effect was observed. When cells were exposed to doxorubicin prior to paclitaxel, either supra-additive, additive or sub-additive effects were seen, depending on the cell line and concentration of paclitaxel used (page 806, right column, second full paragraph). As such, it is apparent that sequence of administration may be an important factor in whether paclitaxel is synergistic with any given antineoplastic agent. Accordingly,

while Applicants appear to have demonstrated unexpected synergistic results as a result of administering paclitaxel and C_6-ceramide to cancer cell lines *in vitro*, the unexpected results are not seen as commensurate in scope with the patent protection sought.

Applicants further argue that neither Jayadev et al. nor Mycek et al. disclose that a combination of paclitaxel and C6-ceramide is or would be expected to show synergistic effects on tumor growth inhibition. However, the Examiner respectfully submits that this teaching is not required to support the instant rejection - all that is required is a reasonable expectation of success. In the instant case, the question is whether one of ordinary skill in the art, with knowledge of the teachings of Jayadev et al. and Mycek et al., would have been motivated to combine paclitaxel and C6-ceramide to treat tumors. In the instant case, Jayadev et al. teach that C_6-ceramide induces dramatic arrest in the G_0/G_1 phase of the cell cycle which results in apoptosis in Molt-4 leukemia cell lines. More importantly, the reference teaches that the effects of C_6-ceramide on cell cycle arrest are a "generalized phenomenon", not restricted to the Molt-4 cell line (page 2049). As such, one skilled in the art would reasonably expect C_6-ceramide to arrest other cell lines in the G_0/G_1 phase of the cell cycle and thereby induce apoptosis. Mycek et al. teach that cytotoxic agents with different toxicities and with different molecular sites and mechanisms of action are usually combined at full doses. With respect to paclitaxel, Mycek et al. teach that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown further favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck, and "several other cancers". In addition, Mycek et al. teach that combination therapy of paclitaxel with other anticancer drugs is being evaluated. Accordingly, one skilled in the art would have been motivated to combine paclitaxel with another agent which

has shown anticancer activity and has a different mechanism of action. C_6-ceramide would have been an obvious choice because it has been shown to arrest cells in the G_0/G_1 phase of the cell cycle and thereby induce apoptosis, and the skilled artisan would have been imbued with at least a reasonable expectation that a combination of C_6-ceramide and paclitaxel would thus result in inhibition of tumor growth.

Secondly, with respect to the 35 U.S.C. 103 rejection of claims 20-41 (now claims 20-33) as being unpatentable over Spencer *et al.* in view of Cai *et al.*, Applicants' arguments are substantially the same as those discussed supra. Accordingly, the Examiner refers to the above response. However, with respect to the specific teachings of the references, Applicants argue that the cited references do not teach the combination of C6-ceramide with paclitaxel or any other anticancer agent. The Examiner respectfully submits that if this explicit teaching was in the references, the present rejection would be made under 35 U.S.C. 102, not 35 U.S.C. 103 as is the case here. The question is whether or not one skilled in the art at the time of the invention would have been motivated to combine C6-ceramide with paclitaxel for the treatment of tumors based on the combined teachings of the cited references. In this case, Spencer et al. teach that paclitaxel is an anticancer agent with broad-spectrum anticancer activity, including activity in treating the specific cancers recited in the instant claims. The reference further teaches combination therapy comprising paclitaxel and several other anticancer agents. As such, one skilled in the art would have been motivated to combine paclitaxel with another anticancer agent. Cai *et al.* provide the motivation to select the instantly claimed C_6-ceramide, wherein they teach that C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells (it is noted that Spencer *et al.* teach that paclitaxel is also effective against breast cancer cells).

As such, one skilled in the art would reasonably expect that paclitaxel and C_6-ceramide, when combined, would be an effective treatment for at least breast cancer. Given the teachings of the cited prior art and the knowledge of one of ordinary skill in the art, the skilled artisan would have been imbued with at least a reasonable expectation that paclitaxel, which has broad-spectrum anticancer activity, would also be effective when combined with another agent that has shown efficacy in inducing apoptosis in a cancer cell line.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 20, 25, and 30-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jayadev *et al.* (J. Biol. Chem., 1995, vol. 270, pages 2047-2052) (prior art of record) in view of Mycek *et al.* (Lippincott's Illustrated Review: Pharmacology 2nd Edition, 1997, pages 376 and 390-392) (prior art of record).

The central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner believes that a *prima facie* case of obvious has been established. Applicants disagree and traverse the present rejection. Applicants' arguments have been fully considered but they fail to persuade the Examiner of error in his determination of obviousness as discussed *supra*.

Jayadev *et al*. teach that C_6-ceramide causes apoptosis in Molt-4 leukemia cells through significant G_0/G_1 arrest (Abstract). The reference also teaches that the effects of C_6-ceramide on cell cycle arrest are a generalized phenomenon, not restricted to the Molt-4 cell line (page 2049).

Mycek *et al*. teach that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown further favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck, and "several other cancers". In addition, Mycek *et al*. teach that combination therapy of paclitaxel with other anticancer drugs is being evaluated.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer C_6-ceramide in combination with paclitaxel as taught by Jayadev *et al*. in view of the teachings of Mycek *et al*. One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Mycek *et al*. motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie*

obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering C_6-ceramide in combination with paclitaxel as taught in Jayadev *et al.* in view of the teachings of Mycek *et al.*, one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Accordingly, the claims are deemed properly rejected under 35 U.S.C. § 103 as being obvious over Jayadev *et al.* in view of Mycek *et al.* As discussed *supra*, Applicant's demonstration of synergism is not commensurate in scope with claims.

Claims 20-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spencer *et al.* (Drugs, 1994, vol. 48, pages 794-847) (prior art of record) in view of Cai *et al.* (J. Biol. Chem., 1997, vol. 272, pages 6918-6926) (prior art of record).

As discussed *supra*, the central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner believes that a *prima facie* case of obvious has been established. Applicants disagree and traverse the present rejection. Applicants' arguments have been fully considered but they fail to persuade the Examiner of error in his determination of obviousness.

Spencer *et al*. teach that paclitaxel has demonstrated broad-spectrum anticancer activity, including activity in treating the specific cancers recited in the instant claims (Table 1). The reference also teaches combination therapy comprising paclitaxel and several other anticancer agents, including cisplatin, cyclophosphamide, doxorubicin, hydroxyurea and dexamethasone (pages 798-799, 805-806 and 821-826). Such combinations are often synergistic as discussed *supra*. With respect to *in vivo* administration, tumor growth inhibition, decreasing size of tumors, and administration routes as recited in claims 20, 22, 24-25, 27, 29, and 31, such *in vivo* administration of paclitaxel to subjects having tumors is taught at page 807, "Activity In Vivo". "[C]remophore-mediated delivery" as recited in claims 23 and 28 is taught at page 807, right column, first full paragraph. Intraperitoneal and subcutaneous administration as recited in claims 24 and 29 is taught at page 807, right column, second full paragraph.

Cai *et al*. teach that C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells (pages 6922-6923; Figure 5).

While the skilled artisan cannot, *a priori*, predict whether a given combination of drugs will have an additive, synergistic, or antagonistic effect, the skilled artisan would reasonably expect that two anticancer agents would, when combined, be effective to treat cancer. As such, it

is, even in the absence of any explicit teachings, *prima facie* obvious to combine two agents known to treat cancer.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer C_6-ceramide in combination with paclitaxel as taught by Spencer *et al.* in view of the teachings of Cai *et al.* One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Spencer *et al.* motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering C_6-ceramide in combination with paclitaxel as taught in Spencer *et al.* in view of the teachings of Cai *et al.*, one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of

cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Accordingly, the claims are deemed properly rejected as being obvious over Spencer *et al*. in view of Cai *et al*. The skilled artisan would have been imbued with at least a reasonable expectation that a combination of paclitaxel and C_6-ceramide would be effective in treating cancer. As discussed *supra*, Applicant's demonstration of synergism is not commensurate in scope with claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614